619. *The Oxidation of Cyclohexanol and Related Compounds with Bromine.*

By I. R. L. Barker, W. G. Overend, and C. W. Rees.

The kinetics of the oxidation of cyclohexanol with bromine in aqueous and mixed solvents are reported. The rate is largely independent of acidity over the pH range 0—7 and there is apparently no general-base catalysis. Little difference in rate was found for the oxidation of *cis*- and *trans*-4-t-butylcyclohexanol, of cholestan-3α- and -3β-ol, and of cyclopentanol and cycloheptanol. A mechanism involving a cyclic transition state is proposed to explain the insensitivity of these oxidations to structural and environmental changes, in striking contrast with bromine oxidation of D-glucose (see preceding Paper).

Aspects of the kinetics of the oxidation of simple alcohols with bromine have been studied by a number of workers.[1-5] The results have been compared, *e.g.*, by Perlmutter-Hayman and his co-workers,[5,6] with those for the corresponding oxidation of D-glucose. We considered it desirable to study the kinetics of the oxidation with bromine of the monohydric alcohols most closely resembling α- and β-D-glucose. The results now reported, taken with those of the preceding Paper, show the superficial comparison of hemiacetals with alcohols to be unjustified. Some of these results have been the subject of preliminary communications.[7]

Experimental

Materials.—Cyclopentanol, cyclohexanol, cycloheptanol, and cyclohexanone were analytical grade and gas-chromatographically homogeneous. *cis*- and *trans*-4-t-Butylcyclohexanol were prepared by Winstein and Holness's method; [8] for the *cis*-isomer the improved hydrogenation of Eliel and Ro [9] was used. The m. p.s [8] and infrared spectra [10] of these compounds, and of cholestan-3α- and -3β-ol, agreed with those in the literature. Aqueous buffered reaction media were as described in the preceding Paper. Bromine, acetic acid, and acetone were analytical grade; the last was used as a 60% (v/v) mixture with the aqueous acetate buffer (0·2M) of pH 5. t-Butyl alcohol (1 l.) was treated with water (100 ml.) containing bromine (2·5 ml.) for 4 hr. at room temperature; the excess of bromine was destroyed with sulphur dioxide, and sodium hydrogen carbonate (4 g.) was added. Fractional distillation gave the azeotrope, 90% (v/v) aqueous t-butyl alcohol, b. p. 79·8—80·0°/760 mm.

Reaction Products.—Cyclopentanone, cyclohexanone, and cycloheptanone were isolated in high yield as the semicarbazones from the bromine oxidation of the corresponding alcohol under kinetic conditions. In acetic acid with cyclohexanone, the first product isolated was dibromocyclohexanone. Cholestan-3-one was isolated in high yield from the oxidation of both cholestan-3-ols in aqueous t-butyl alcohol; *e.g.*, bromine (8×10^{-4} mole) in water (15 ml.) was added to the α-epimer (0·2 g., 5×10^{-4} mole) in 75% (v/v) t-butyl alcohol–water (100 ml.). The mixture was stored for 12 hr., then warmed to 60°. Bromine was destroyed with sulphur dioxide, t-butyl alcohol was removed by steam-distillation, and extraction of the residue with chloroform gave cholestan-3-one (0·16 g.), m. p. (from methanol) and mixed m. p. 127—128°.

Kinetic Measurements.—Reaction rates were obtained by following (*a*) the disappearance of bromine or (*b*) the appearance of cyclohexanone.

(*a*) In most experiments aliquots of the reaction mixture were added to sodium arsenite

[1] Bugarszky, *Z. phys. Chem.*, 1901, **38**, 561; 1903, **42**, 545.
[2] Farkas, Perlmutter, and Schächter, *J. Amer. Chem. Soc.*, 1949, **71**, 2827, 2829, 2833.
[3] Kaplan, *J. Amer. Chem. Soc.*, 1958, **80**, 2639.
[4] Swain, Wiles, and Bader, *J. Amer. Chem. Soc.*, 1961, **83**, 1945.
[5] Perlmutter-Hayman and Weissmann, *J. Amer. Chem. Soc.*, 1962, **84**, 2323.
[6] Perlmutter-Hayman and Persky, *J. Amer. Chem. Soc.*, 1960, **82**, 276.
[7] Barker, Overend, and Rees, *Chem. and Ind.*, 1961, 558; 1962, 463.
[8] Winstein and Holness, *J. Amer. Chem. Soc.*, 1955, **77**, 5562.
[9] Eliel and Ro, *J. Amer. Chem. Soc.*, 1957, **79**, 5992.
[10] Pickering and Price, *J. Amer. Chem. Soc.*, 1958, **80**, 4931.

solution containing sodium hydrogen carbonate, and the excess of arsenite was determined iodometrically. However, in the presence of substantial amounts of acetone or t-butyl alcohol (from the reaction medium) the starch–iodine complex was not formed, and these solvents were first removed by steam-distillation. Blank determinations established that steam-distillation of the arsenite solution did not alter the iodine titre. For reactions in acetic acid, analysis with sodium arsenite was unsatisfactory, so the aliquots were added to an excess of aqueous potassium iodide, the iodine liberated being determined with standard sodium thiosulphate.

(*b*) For the analysis of cyclohexanone in dilute aqueous solution containing cyclohexanol, Maslennikov's method,[11] based on spectrophotometric estimation of the azo dye formed by coupling cyclohexanone (1 mole) with diazotised H-acid (2 moles), was used. If great care was taken to standardise the procedure, and reagents were freshly prepared for each run, the results were good. All analyses were performed in duplicate or triplicate, as follows: to the solution to be analysed (5 ml.), containing cyclohexanone ($1—40 \times 10^{-6}$ g. ml.$^{-1}$), was added successively 10% aqueous hexamethylenetetramine (1 ml.), three drops of acetic anhydride, 1% aqueous sodium pyrosulphite (1 ml.), 25% aqueous sodium hydroxide (1 ml.), and a freshly prepared solution of the diazonium salt of H-acid (2 ml.) (made by adding 2 ml. of 1% aqueous sodium nitrite to 5 ml. of a 0·25% solution of H-acid in 0·1N-sulphuric acid). After 5 min., the mixture was diluted to 50 ml. with water, and the optical density at 550 mμ measured against the appropriate blank solution. In these experiments the reaction was stopped by adding the aliquot to excess of sodium sulphite solution.

Kinetic Results.—These are summarised in Tables 1—6. The oxidation of cyclohexanol to cyclohexanone with bromine in dilute aqueous solution is first-order in cyclohexanol; Table 1 shows typical results, for the acetate buffer of pH 5, where the concentration of cyclohexanone was determined spectrophotometrically. Cyclohexanone reacts with bromine at about 1/30th

TABLE 1.

Reaction between cyclohexanol (0·005M) and bromine (0·05M) in aqueous buffer of pH 5, at 20°.

Time (min.)	2·9	5·0	7·2	9·9	14	18	23·1	28	∞
Optical density	0·142	0·231	0·315	0·400	0·507	0·581	0·667	0·728	0·900
10^2k_2 (l. mole^{-1} sec.$^{-1}$)	1·96	1·98	1·99	1·98	1·97	1·92	1·95	1·97	—

Mean $k_2 = 1·97$; k_2 obtained graphically = 1·99 (l. mole^{-1} sec.$^{-1}$).

TABLE 2.

Reaction between cyclohexanol (0·005M) and bromine (0·05M) in aqueous buffer of pH 5.

Temp.	0°	10	20	E_{act} = 19·3 kcal. mole^{-1}
10^3k_2 (l. mole^{-1} sec.$^{-1}$)	1·78	6·34	19·9	

TABLE 3.

Reaction between bromine (0·004M) and cyclohexanol (0·05M) in aqueous buffers at 20°.

pH	0	1	2	3	4	5	6	7
10^2k_2 (l. mole^{-1} sec.$^{-1}$)	1·8	1·9	1·9	1·9	2·0	1·7	1·2	1·1

of the rate with cyclohexanol under these conditions, and hence this subsequent reaction could be ignored. The optical density for t_∞, used in calculating k_2 by the integrated equation, was obtained from a standard solution of cyclohexanone. The Arrhenius energy of activation given in Table 2 was obtained graphically. Rate coefficients for reactions with bromine in deficiency showed the characteristic decrease, as the reaction proceeded, caused by conversion of active free bromine into inactive tribromide ions by the bromide ions produced. In these cases rate constants were obtained by measurement of initial slopes from concentration–time curves. Second-order rate constants for the oxidation of cyclohexanol over the pH range 0—7 are given in Table 3.

[11] Maslennikov, *Zhur. analit. Khim.*, 1958, **13**, 599 (*Analyt. Abs.*, 1959, **6**, 1378).

TABLE 4.

Reactions between bromine (0·004M) and the cycloalkanols (0·005M) in mixed solvents.

	10^2k_2 (l. mole^{-1} sec.$^{-1}$)		
Cycloalkanol	" 50% " t-Butyl alcohol at 25°	" 75% " t-Butyl alcohol at 20°	" 60% " Acetone at 0° *
Cyclohexanol	2·72	1·17	—
cis-4-t-Butylcyclohexanol	2·92	1·24	0·86
trans-4-t-Butylcyclohexanol	2·26	0·99	0·76
Cholestan-3α-ol	—	2·26	—
Cholestan-3β-ol	—	1·92	—

* Cycloalkanol concentration = 0·05M.

TABLE 5.

First-order rate constants for the reaction of bromine (0·005M) with the cyclohexanol (0·05M) in acetic acid at 24·65°.

	10^5k_1 (sec.$^{-1}$)
Cyclohexanol	4·61
cis-4-t-Butylcyclohexanol	5·57
trans-4-t-Butylcyclohexanol	4·49

TABLE 6.

Reaction between bromine (0·005M) and the cycloalkanols (0·01M) in the aqueous acetate buffer of pH 5, at 20°.

	10^2k_2 (l. mole^{-1} sec.$^{-1}$)
Cyclopentanol	0·766
Cyclohexanol	1·78
Cycloheptanol	5·97

To measure the oxidation rates for the other alcohols mixed solvents were necessary. The following (volume %) were used: 50% t-butyl alcohol–50% aqueous acetate buffer, pH 5; 75% t-butyl alcohol–25% water; 60% acetone–40% aqueous acetate buffer, pH 5; these are referred to as " 50% " t-butyl alcohol, " 75% " t-butyl alcohol, and " 60% " acetone, respectively. The first solvent reacted with bromine negligibly slowly, but a correction for this reaction was necessary with the others, particularly aqueous acetone. Results for these solvent systems are given in Table 4.

In acetic acid the oxidation of cyclohexanol was first-order in total bromine ($Br_2 + Br_3^-$); it was followed by the much faster bromination of cyclohexanone. The oxidation rate could not be followed by analysis of the product, since the dibromocyclohexanone formed did not couple with diazotised H-acid. The reaction between cyclohexanone (0·05M) and bromine (0·005M) in acetic acid at 25° was too fast to be measured by the present method; it was virtually complete within 3 minutes. The first-order rate constants given in Table 5 are based on the total consumption of bromine by the cyclohexanols in acetic acid. Oxidation rates for cyclopentanol, cyclohexanol, and cycloheptanol, under the same conditions, were calculated from initial slopes (Table 6).

DISCUSSION

In the oxidation of cyclohexanol to cyclohexanone with bromine in dilute aqueous solution we find similar kinetics to those reported for simple acyclic alcohols.[1,2,4,5] Thus, the reaction is first-order in cyclohexanol and in free bromine; the rate coefficients diminish steadily as the reaction proceeds, owing to the conversion of bromine into the inert tribromide ion, unless bromine is in large excess. The loss of bromine to cyclohexanone is negligible under these conditions. The reaction obeys the Arrhenius equation.

The rate is independent of acidity over the pH range 0—5, but is somewhat decreased at pH 6—7 (Table 3); this is ascribed to a shift in the hydrolytic equilibrium of bromine, converting significant amounts of bromine into bromide and hypobromous acid at the higher pH. Furthermore, the rate is independent of the nature and concentration of the buffer ions, which ranged from the weakly basic sulphate and hydrogen sulphate ions to the more strongly basic acetate, dihydrogen phosphate, and monohydrogen phosphate ions.

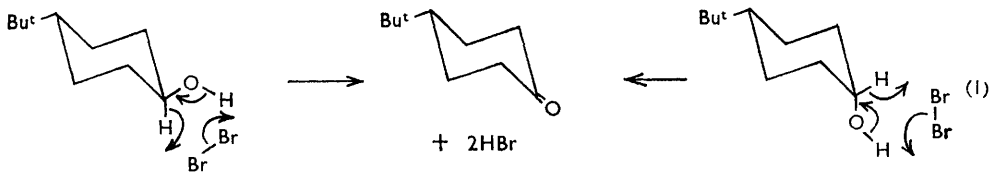
The oxidation of cyclohexanol in aqueous t-butyl alcohol followed the same kinetics as in water. It is noteworthy that the oxidation rate in the aqueous phosphate buffer of

pH 6 was nearly identical with that in " 65% " and " 75% " t-butyl alcohol (10^2k_2 = 1·20, 1·18, and 1·17, respectively, at 20°) despite the substantial change in dielectric constant.

The oxidation of cyclohexanol with bromine in acetic acid was exceptional, however; the reaction was first-order in bromine, there being no fall in rate constant caused by formation of tribromide ions. This is presumably attributable to the virtual absence of bromide ions, and hence tribromide ions, in this very poorly ionising solvent; the ionisation constant [12] for hydrogen bromide in acetic acid is only $1·9 \times 10^{-7}$. This reaction was exceptional also in that the product was a dibromocyclohexanone; the oxidation step was rate-determining, followed by rapid bromination of cyclohexanone.

The bromine oxidation of conformationally pure *cis*- and *trans*-4-t-butylcyclohexanol [8] in aqueous t-butyl alcohol, aqueous acetone, and acetic acid was kinetically very similar to that of cyclohexanol, and led to the same result (Tables 4 and 5); the *cis*-isomer (axial hydroxyl group) is oxidised 20—30% faster than the *trans*-isomer (equational hydroxyl group). It may be concluded that there is very little stereochemical requirement on the part of the alcohol in this bromine oxidation. Precisely the same pattern of reactivity is found with cholestan-3α- and -3β-ol, where the locked conformation permits no ambiguity about the axial and equatorial disposition, respectively, of the hydroxyl groups. In " 75% " t-butyl alcohol the axial alcohol is again oxidised very slightly faster (18%) than its epimer (Table 4). These rates are very much less sensitive to the configuration of the hydroxyl group than are the rates of oxidation with chromic acid,[8,13,14] where the greater overall rate of the axial epimer results from the part played by fission of an equatorial C–H bond in the chromate ester intermediate.[8,15] The present bromine oxidations cannot involve the analogous ester intermediates, the hypobromites, in a pre-equilibrium stage, since in their formation protons are liberated [R_2·CH·OH + Br_2 ⇌ R_2·CH·OBr + H^+ + Br^-] and dependence upon acidicity would follow. As shown above, the oxidation rate is independent of acid concentration from pH 0 to 5 for cyclohexanol.

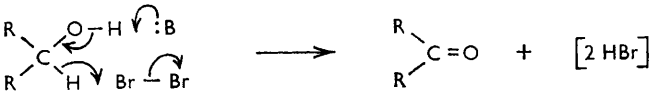
The mechanism of the reaction between these cycloalkanols and bromine must, therefore, involve one molecule of each in the transition state, must explain the insensitivity of the rate to acid concentration, to the nature of the buffer, to a change from fully aqueous to mixed solvents, and to the configurational disposition of the hydroxyl group, and must explain the very small but consistently greater reactivity of epimers with axial hydroxyl groups. We propose a concerted mechanism (1) with a six-membered cyclic transition state, which is consistent with all these facts.



The very similar reactivity of epimeric pairs of alcohols (and indeed of all the alcohols investigated here) follows if the accessibility of both the hydroxyl group and the hydrogen atom, at the reaction centre, are about equally important. The slightly faster oxidation of the epimer with the axial hydroxyl group would result from the greater release of steric strain in this case on passing from the initial to the transition state. This cyclic mechanism is further supported by the observation [4] of both O–H and C–H kinetic isotope effects in the bromine oxidation of propan-2-ol in water. On the basis of their results

[12] Smith and Elliott, *J. Amer. Chem. Soc.*, 1953, **75**, 3566.
[13] Schreiber and Eschenmoser, *Helv. Chim. Acta*, 1955, **38**, 1529.
[14] Richer, Pilato, and Eliel, *Chem. and Ind.*, 1961, 2007.
[15] Barton, *Experientia*, 1950, **6**, 316; *J.*, 1953, 1035.

the authors favour an acyclic mechanism (2) involving rate-determining transfer of a hydride ion from carbon to bromine.



(2)

We consider that the evidence summarised above strongly favours the cyclic (1) over the acyclic mechanism (2). In particular, the second mechanism does not explain the insensitivity to configuration and to environment which appears to characterise these bromine oxidations. Reactions which involve rate-determining attack on a group equatorially or axially disposed usually show [15] considerably greater rate differences than these, and a small variation of rate with change of reaction medium has often been used as evidence of a cyclic mechanism (see, *e.g.*, ref. 16). For the same reasons Kaplan's mechanism,[3] where dissociation of an ethanol–bromine complex into HBr_2^- and the conjugate acid of acetaldehyde is rate-determining, is considered to be inadequate.

The present results for the bromine oxidation of cyclohexanols show important differences from those for D-glucose described in the preceding Paper. β-D-Glucose, with the C-1 hydroxyl group equatorial, is oxidised very much faster than α-D-glucose, with this group axial, in complete contrast to the 4-t-butylcyclohexanols. Further, the rate of oxidation of D-glucose is strongly dependent upon acid concentration over the pH range 2—7; that of cyclohexanol is not. This contrast supports the entirely different mechanisms proposed, in this and the preceding Paper, for the oxidation of the cycloalkanols and the sugars, and vitiates the direct comparison of their reactivities.

Department of Chemistry, Birkbeck College, Malet Street, London W.C.1.
King's College, Strand, London W.C.2. [*Received, November 1st*, 1963.]

[16] Westheimer and Jones, *J. Amer. Chem. Soc.*, 1941, **63**, 3283.